Arthritis Advisory Committee

December 1, 1998

NDA 20-998 Celebrex™ (celecoxib) Searle

Volume I: FDA Medical Reviews

Rheumatoid Arthritis

Statistical Review

Statistical Review and Evaluation

DRAFT

NDA20-998
Name of Drug: SC-58635
Applicant: G. D. Searle and Co.
Indication: Treatment of Signs and Symptoms of Osteoarthritis and Rheumatoid Arthritis, Management of Pain, and Improvement of Gastrointestinal Safety
Documents Reviewed: RA Part of Statistical Section (Vol.258-Vol.339) of NDA20-998 Dated 6/30/98 by CDER
Reviewer: Laura Lu, Ph.D.
Date of Review: 10/30/98

I. Introduction

NDA20-998 has been submitted for approval of SC-58635 for treatment of signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA), management of pain, and improvement of gastrointestinal (GI) safety. This review focuses on the indications of treatment of RA and GI safety.

Two pivotal studies and five supportive studies were conducted in patients with RA. The two phase-III pivotal studies (022, 023) were double blind, placebo-controlled trials of 12 weeks duration. Among the 5 supportive studies, Study 012 was a Phase-II study; Studies 041, 062, and 071 were double blind Phase-III studies; and Study 024 was a open labeled phase-III study. For efficacy results, this reviewer will focus on Studies 022 and 023. For Gastrointestinal (GI) safety results, this reviewer will focus on Studies 022 and 041. GI Studies 062 and 071 were conducted in both OA and RA patients and are reviewed by Dr. Ping Gao.

II. Efficacy Studies in RA patients

1. Study 022

1). Protocol

This was a double-blind, placebo-controlled, multi-center, parallel group, 12 weeks flared study for the comparison of the efficacy and UGI safety of SC-58635 (100 mg BID, 200 mg BID, 400 mg BID) versus placebo and Naproxen 500 mg BID in patients with RA.

A total of 1000 patients were to be recruited with 200 patients in each treatment group. Primary measures of arthritis efficacy were the ACR-20 Responder Index, Patient's Global Assessment of Arthritic Condition, Number of Tender/Painful Joints, Number of Swollen Joints, and Physician's Global Assessment of Arthritic Condition. Secondary measures of arthritis efficacy were Patient's Assessment of Pain-Visual Analog Scale (VAS), Tender/Painful Joints Score, Swollen Joints Score, Duration of Morning Stiffness, Health Assessment Questionnaire (HAQ) Functional Disability Index,

measurement of C-Reactive Protein (CRP), Incidence of Withdrawal Due to Lack of Arthritis Efficacy, Time to Withdrawal Due to Lack of Arthritis Efficacy, and the ACR-50 Responder Index. The above arthritis assessments were performed at the screening and baseline visits and at Weeks 2, 6 and 12 (or Early Termination) follow-up visits. The UGI safety of SC-58635 was assessed with endoscopies performed at baseline and Week 12 (or Early Termination). Quality of Life analysis consisted of the SF-36 Health Survey which was performed at baseline and Week 12 (or Early Termination Visit).

Physician's and Patient's Global Assessments of Arthritic Condition were graded on the following scale: 1 = very good; 2 = good; 3 = fair; 4 = poor; and 5 = very poor. A patient was classified as "improved" if a reduction of at least two grades from baseline for grades 3 to 5 or a change in grade 2 to 1 was observed. A patient was classified as "worsened" if an increase of at least two grades from baseline for grades 1 to 3 or a change in grade 4 to 5 was observed. The 'improved' rates and 'worsened' rates were analyzed by the CMH Test stratified by center. The linear trend test (Naproxen group excluded) and pairwise comparisons were performed based on the above CMH tests.

Mean change analyses, including the linear trend test for all SC-58635 and placebo groups and overall and pairwise comparisons for all five treatment groups, were performed on all primary measures of efficacy with the exception of the ACR-20 responder index, using an analysis of covariance (ANCOVA) with treatment and center as factors, and the corresponding baseline value as a covariate. ACR-20 Responder Index was analyzed by the CMH Test stratified by center. The results of the pairwise comparisons for the SC-58635 200 mg BID and 400 mg BID treatment groups versus placebo for the ITT Cohort were interpreted using Hochberg's step-up procedure.

2). Study Results

Patient Disposition

A total of 1149 patients were enrolled into the study and 1148 received treatment for up to 12 weeks as follows: 231 patients in the placebo group, 240 patients in the SC-58635 100 mg BID group, 235 patients in the SC-58635 200 mg BID group, 217 patients in the SC-58635 400 mg BID group, and 225 patients in the Naproxen 500 mg BID group.

Of the 1148 patients in the ITT Cohort, 698 (61%) completed the study: 101 (44%) in the placebo group, 154 (64%) in the SC-58635 100 mg BID group, 158 (67%) in the SC-58635 200 mg BID group, 137 (63%) in the SC-58635 400 mg BID group, and 138 (61%) in the Naproxen 500 mg BID group. The main reasons for study termination were treatment failure and adverse events. Placebo group had noticeably more patients withdrew due to treatment failure (45%) than other treatment groups (28% in SC-58635 100 mg BID, 21% in SC-58635 200 mg BID, 27% in SC-58635 400 mg BID, and 29% in Naproxen 500 mg BID.). The reasons for study termination, groups by treatment, for all randomized patients are summarized in Table 1 of Appendix A.

Demographics and Baseline Characteristics

The distributions of patients in age, race, gender, height, weight, vital signs, and systolic and diastolic blood pressures at baseline were similar among the treatment groups ($p \geq 0.1$).

Efficacy Results

The following results are for the intent-to-treat cohort.

ACR Response Index

The results for ACR Response Index described below are also listed in Table 2 of Appendix A.

SC58635 vs. placebo: Based on the ACR-20 Responder Index, more patients in the SC-58635 treatment groups were classified as 'improved' (responders) compared to the placebo group at Weeks 2, 6, and 12. After adjusted for multiple comparison, the results showed that the number of patients classified as 'improved' were statistically significantly higher in both SC-58635 200 mg BID and SC-58635 400 mg BID than in placebo at Weeks 2, 6, and 12 ($p \leq 0.012$). In addition, the number of patients classified as improved in the SC-58635 100 mg BID group was also statistically significantly higher than in placebo at Weeks 2, 6, and 12 ($p \leq 0.008$).

Naproxen vs. placebo and SC-58635: More patients in the Naproxen 500 mg BID group improved at Weeks 2, 6, and 12 compared to placebo and this difference in the distribution of patients who improved was statistically significant at each of these time points ($p \leq 0.049$). At Weeks 2 and 6, there were statistically significantly fewer patients who improved in the Naproxen 500 mg BID group versus the SC-58635 200 mg BID group ($p \leq 0.028$). There were no other statistically significant differences in the distribution of patients who improved between the Naproxen group and the SC-58635 treatment groups ($p \geq 0.076$).

Among SC-58635 groups: SC-58635 groups were generally comparable in ACR improvement rate except that the 200 mg BID group showed statistically significantly higher improvement rate than the 100 mg BID group and 400 mg BID group at Week 6 ($p = .038, .047$, respectively).

ACR Individual Components

The results of the comparison between SC-58635, placebo and Naproxen in ACR individual components described below are also listed in Tables 3-9 of Appendix A.

SC58635 vs. placebo: After adjusted for multiple comparison, the results showed that SC-58635 200 mg BID and 400 mg BID were statistically superior to placebo at all post-baseline time points (Weeks 2, 6, and 12) by both categorical change and mean change analyses in all ACR individual components except CRP. In addition, SC-58635 100 mg BID were statistically superior to placebo at all post-baseline time points by both categorical change and mean change analyses in all ACR individual components except CRP and HAQ.

No statistical significance was found between SC-58635 (100 mg BID, 200 mg BID, and 400 mg BID) and placebo in CRP measurements at any time points (week 2, week 6, and week 12). Also, no statistical significance was found between SC-58635 100 mg BID and placebo at Week 12 (p=0.088) in HAQ.

Naproxen vs. placebo and SC-58635: Except for Number of Tender/Painful Joint at Week 12 and CRP at all post-baseline time points, ACR individual components of Naproxen 500 mg BID were statistically superior to placebo at all post-baseline time points. In general, Naproxen 500 mg BID and SC-58635 (100 mg BID, 200 mg BID, and 400 mg BID) were not statistically significantly different in ACR individual components. Two noticeable patterns were that Naproxen 500 mg BID had statistically significantly more (or less deterioration) improvement in CRP than SC-58635 400 mg BID at Week 2 and Week 6 (p=.007 and .021, respectively), and more improvement in Physician's Global than SC-58635 200 mg BID at Week 2, Week 6 and Week 12 (p=.003, .023 and .034, respectively). _

Among SC-58635 groups: The results for ACR individual components were comparable for the SC-58635 200 mg BID and 400 mg BID. SC-58635 200 mg BID was numerically better than SC-58635 100 mg BID at all time points in all ACR individual components, and SC-58635 200 mg BID was also statistically superior to SC-58635 100 mg BID in Patients Global and Physician's Global at Week 2 and Week 6 ($p \leq .048$), and in HAQ score at Week 6 and Week 12 (p=.026 and .008, respectively).

ACR 50

A patient was classified as improved if there was at least a 20% improvement from baseline in the number of tender/painful joints and in the number of swollen joints **and** a 50% improvement from Baseline in at least three of the following: Physician's Global Assessment of Arthritic Condition, Patient's Global assessment of Arthritic Condition, Patient's Assessment of Pain, C-Reactive Protein, and HAQ Functional Disability Index.

The results of the analysis of the ACR-50 Responder Index are presented in Table 10 of Appendix A. The trend in ACR-50 Responder Index among treatment groups were similar to that in ACR-20 Responder Index with the pairwise comparison showing superiority of SC-58635 200 mg BID and 400 mg BID groups over the placebo group, and no statistically significantly difference between the SC-58635 groups and Naproxen group.

Quality of Life Measurements

After adjusted for multiple comparison, the results showed that SC-58635 200 mg BID and 400 mg BID were statistically superior to placebo at Week 12 in all domains of SF-36 (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) ($p \leq 0.047$). SC-58635 100 mg BID was statistically superior to placebo at Week 12 only in Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional ($p \leq 0.027$).

Naproxen 500 mg BID was statistically superior to placebo at Week 12 in all domains of SF-36 ($p \leq 0.024$) except Role-Physical ($p=0.097$).

Naproxen 500 mg BID was comparable to SC-58635 (100 mg BID, 200 mg BID, and 400 mg BID) in all SF-36 domains.

Safety Results

Tables 11-14 of Appendix A listed the pooled (Studies 022 and 023) incidences of adverse events that are statistically significantly different among treatment groups. If the total incidences of adverse events in a body system are statistically significantly different among treatment groups, the individual terms of adverse events in that body system are also listed. Tables 11, 12, 13 and 14 listed the incidences of all adverse events, adverse events that are treatment-related, severe adverse events and treatment-related severe adverse events, respectively, that are statistically significantly different across treatment groups by treatment group, body system and ICD-9 Code. Although the statistical significance were caused mainly by the higher adverse event rates in SC-58635 groups and Naproxen group, placebo had higher incidences in Back Pain, Pain and Nausea, which might be disease related instead of treatment related.

2. Study 023

1). Protocol

The protocol of Study 023 was identical to that of Study 022 except that UGI safety was not evaluated.

2). Study Results

Patient Disposition

A total of 1103 patients were enrolled at 75 sites in this study and were randomized to receive one of the five treatments for 12 weeks: placebo, 221 patients; SC-58635 100 mg BID, 228 patients; SC-58635 200 mg BID, 219 patients; SC-58635 400 mg BID, 217 patients; Naproxen 500 mg BID, 218 patients. Of the 1103 patients enrolled, a total of 1102 patients received at least one dose of study drug and were included in the ITT

Cohort. Of the 1102 patients in the ITT Cohort, 578 (52%) completed the study: 78 (35%) in the placebo group, 117 (51%) in the SC-58635 100 mg BID group, 124 (57%) in the SC-58635 200 mg BID group, 126 (58%) in the SC-58635 400 mg BID group, and 133 (61%) in the Naproxen 500 mg BID group. Placebo group had noticeably more patients withdrew due to treatment failure (57%) than other treatment groups (40% in SC-58635 100 mg BID, 34% in SC-58635 200 mg BID, 32% in SC-58635 400 mg BID, and 32% in Naproxen 500 mg BID.). Table 1 of Appendix A presents the reasons for study termination, grouped by treatment, for all randomized patients.

Demographics and Baseline Characteristics

There was a statistically significant difference in mean age across treatment groups (p=0.017), but further exploratory analysis did not indicate a statistically significant age by treatment interaction. The treatment groups were comparable in gender, height, weight, vital signs, and systolic and diastolic blood pressures at baseline.

Efficacy Results

The following results are for the intent-to-treat cohort.

APPEARS THIS WAY
ON ORIGINAL

ACR Response Index

The results for ACR Responder Index described below are also listed in Table 2 of Appendix A.

SC-58635 vs. placebo: Based on the ACR-20 Responder Index, more patients in the SC-58635 treatment groups were classified as improved compared to the placebo group at Weeks 2, 6, and 12. After adjusted for multiple comparison, the results showed that the differences in the distribution of patients classified as improved were statistically significant for both SC-58635 200 mg BID and SC-58635 400 mg BID compared to placebo at Weeks 2, 6, and 12 ($p \leq 0.002$). In addition, the percentage of patients classified as improved in the SC-58635 100 mg BID group was statistically significantly higher than placebo at Weeks 2, 6, and 12 ($p \leq 0.015$).

Naproxen vs. placebo and SC-58635 groups: More percentage of patients in the Naproxen 500 mg BID group improved at Weeks 2, 6, and 12 compared to placebo and this difference was statistically significant at each of these time points ($p \leq 0.001$). With the exception of Naproxen compared to SC-58635 100 mg BID at Week 12 (p=0.011), there were no statistically significant differences between the Naproxen group and the SC-58635 treatment groups in the percentage of patients classified as improved ($p \geq 0.096$).

Among SC-58635 groups: SC-58635 groups were generally comparable in ACR improvement rate except that the 200 mg BID group showed statistically significantly higher improvement rate than the 100 mg BID group at Week 12 (p=.038).

ACR Individual Components

The results of the comparison between SC-58635, placebo and Naproxen in ACR individual components described below are also list in Tables 3-9 of Appendix A.

SC-58635 vs. placebo: Except for CRP and Number of Swollen Joints, the results in ACR individual components of SC-58635 100 mg BID, 200 mg BID and 400 mg BID were statistically superior to placebo at all post-baseline time points by both categorical change and mean change analyses ($p \leq .103$). In CRP, no statistical significance was found between SC-58635 (100 mg BID, 200 mg BID, and 400 mg BID) and placebo at any post-baseline time points ($p > .06$) by mean change analyses. In Number of Swollen Joints, statistical significance were only found between SC-58635 100 mg BID and placebo by categorical change analysis at Week 2 ($p = .003$) and Week 12 ($p = .002$).

Naproxen vs. placebo and SC-58635: The results in all ACR individual components of Naproxen 500 mg BID were statistically superior to placebo at all post-baseline time points (week 2, week 6, and week 12). Naproxen 500 mg BID was statistically superior ($p \leq 0.042$) to SC-58635 100 mg BID at all time points in Patient's Global Assessment, Physician's Global Assessment, and at Week 2 and Week 12 in Patient's Assessment of Arthritis Pain, and at Week 12 in HAQ score. Naproxen 500 mg BID was also statistically superior ($p \leq 0.018$) to SC-58635 400 mg BID at all time points in CRP.

Among SC-58635 groups: The results in ACR individual components were comparable for SC-58635 200 mg BID and 400 mg BID except that the 200 mg BID had significantly more improvement in CRP ($p = .008$) than the 400 mg BID group at Week 6. SC-58635 200 mg BID was numerically better than SC-58635 100 mg BID at all time points in all ACR individual components, and SC-58635 200 mg BID was also statistically superior to SC-58635 100 mg BID in Patients Global, Patient's Assessment of Arthritis Pain at Week 2 and Week 12 ($p \leq .042$), HAQ score at Week 6 and Week 12 ($p \leq .031$), and Physician's Global and Number of Tender/Painful Joint at Week 2 ($p \leq .046$).

ACR 50

The results of the analysis of the ACR-50 Responder Index are presented in Table 10 of Appendix A. The trend in ACR-50 Responder Index among treatment groups were similar to that in ACR-20 Responder Index with the pairwise comparison showing superiority of SC-58635 200 mg BID and 400 mg BID groups over the placebo group, and no statistically significant difference between the SC-58635 200 mg BID, SC-58635 400 mg BID groups and Naproxen group.

Quality of Life Measurements

All three SC-58635 treatment groups showed statistically significantly more improvement than placebo in Physical Functioning, Role Physical, Bodily Pain, Vitality,

Social Functioning, and Mental Health domains ($p \leq 0.033$), but none of them showed statistically significantly more improvement than placebo in General Health and Role-Emotional. Placebo showed numerically more improvement in Role-Emotional than SC-58635 100 mg BID.

Naproxen 500 mg BID showed statistically significantly more improvement than placebo in Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, and Mental Health domains ($p \leq 0.004$).

No statistically significant differences were found between Naproxen 500 mg BID and SC-58635 groups in all quality of life domains. ($p \geq 0.074$).

Safety Results

See the discussion in Study 22 in page 5.

III. GI Studies in RA patients

1. GI Endpoints and Analyses Plan

1). Study 022

The UGI safety of SC-58635 was evaluated with endoscopies performed at baseline and exit time (Week 12 or early termination). Separate gastric and duodenal mucosal scores were assigned to each patients at each visit (0: no visible lesions (normal mucosa); 1:1-10 petechiae; 2: >10 petechiae; 3:1-5 erosions; 4: 6-10 erosions; 5: 11-25 erosions; 6: >25 erosions; 7: Ulcer).

A 'Week 12' analysis and a 'Final' analysis were done for the crude rates of gastroduodenal ulcers (i.e., a gastric or duodenal score of 7), gastric ulcers, and duodenal ulcers with CMH tests stratified by baseline status. In the 'Week 12' analysis, only patients undergoing endoscopy at Week 12 and patients found to have an ulcer before Week 12 were included, and last-observation-carried-forward approach was used in calculating the Week 12 ulcer rates among these patients. Patients were categorized as unknown and not included in the Week 12 analysis when they did not undergo an endoscopy at Week 12 and no ulcer was found before Week 12. In the 'Final' analysis, all patients who underwent endoscopy at a scheduled visit or an early termination visit were included and last-observation-carried-forward approach was used in calculating the final ulcer rates. Only those patients who did not undergo a final endoscopy were categorized as unknown and therefore not include in the "Final' analysis.

Time to ulcer was analyzed by log-rank tests. Cumulative ulcer rate based on Kaplan-Meier methods was calculated at Week 12. Patients who withdrew from the study because of reasons other than the development of gastric, duodenal or pyloric channel ulcer were censored at withdrawal time. Patients who completed the study without an

ulcer were censored at the final visit.

2). Study 041

Study 041 was a randomized, double-blind, multi-center, parallel trial designed to evaluate the efficacy and GI safety of SC-58635 200 mg BID as compared to Diclofenac SR 75 mg BID in treating the signs and symptoms of RA. For this study, this reviewer concentrates on the review of GI safety.

A total of 430 patients (212 in the SC-58635 200 mg BID group and 218 in the Diclofenac SR 75 mg BID group), instead of 288 patients as planned in the protocol, were scheduled for endoscopy examination at baseline and Week 24 (or Early Termination). Only a 'Final' analysis was done for the ulcer rate.

2. GI Safety Results

1). Study 022

APPEARS THIS WAY
ON ORIGINAL

Gastroduodenal Endoscopy Results

The gastroduodenal endoscopy results by 'Final' and 'Week 12' analyses described below are also presented in Table 15 of Appendix A.

Based on the 'Final' analysis, ulcers developed in 4 (2%) placebo patients, 9 (4%) SC-58635 100 mg BID patients, 6 (3%) SC-58635 200 mg BID patients, 8 (4%) SC-58635 400 mg BID patients and 37 (18%) Naproxen 500 mg BID patients. The incidence of ulceration was significantly greater in the Naproxen 500 mg BID group than all other treatment groups ($p<0.001$) and there were no statistically significant differences between placebo and any of the SC-58635 groups ($p\geq0.200$). Further, there was no statistically significant difference in the incidence of ulceration between any of the SC-58635 groups ($p\geq0.526$).

Based on the 'Week 12' analysis, ulcers developed in 4 (4%) placebo patients, 9 (6%) SC-58635 100 mg BID patients, 6 (4%) SC-58635 200 mg BID patients, 8 (6%) SC-58635 400 mg BID patients and 36 (26%) Naproxen 500 mg BID patients. Results of pairwise comparisons were consistent with that of the 'Final analysis.

Based on the Kaplan-Meier estimator, the rate of developing gastroduodenal ulceration was greater for Naproxen than for placebo or any of the SC-58635 treatment groups and this difference was statistically significant ($p<0.001$). There were no statistically significant differences between placebo and any of the SC-58635 groups ($p\geq0.487$) and there were no statistically significant differences among any of the SC-58635 groups ($p\geq0.348$). The estimated cumulative ulcer rates at Week 12 were: 4.2% for placebo, 11.5% for SC-58635 100 mg BID, 7.5% for SC-58635 200 mg BID, 9.9% for SC-58635 400 mg BID, and 37.4% for Naproxen 500 mg BID (Figure 1).

Gastric Endoscopy Results

The gastric endoscopy results by 'Final' and 'Week 12' analyses described below are also presented in Table 16 of Appendix A.

Based on the 'Final' analysis, ulcers developed in 3 (2%) placebo patients, 6 (3%) SC-58635 100 mg BID patients, 4 (2%) SC-58635 200 mg BID patients, 7 (4%) SC-58635 400 mg BID patients and 30 (14%) Naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in Naproxen 500 mg BID compared with all other treatment ($p<0.001$) and there were no statistically significant differences between placebo and any SC-58635 groups ($p\geq0.254$). Further, there was no statistically significant difference in the incidence of ulceration between any of the SC-58635 groups ($p\geq0.404$).

Based on the 'Week 12' analysis, ulcers developed in 3 (3%) placebo patients, 6 (4%) SC-58635100 mg BID, 4 (3%) SC-58636 200 mg BID patients, 7 (5%) SC-58635 400 mg BID patients and 29 (22%) Naproxen 500 mg BID patients. The results of the pairwise comparisons were consistent with that of the 'Final' analysis.

Based on the Kaplan-Meier estimator, the rate of developing gastric ulceration was greater for Naproxen than for placebo or any of the SC-58635 groups and this difference was statistically significant ($p<0.001$). There were no statistically significant differences between placebo and any of the SC-58635 groups ($p\geq0.394$) and there were no statistically significant differences among any of the SC-58635 groups ($p\geq0.201$).

Duodenal Endoscopy Results

The duodenal endoscopy results by 'Final' and 'Week 12' analyses described below are also presented in Table 17 of Appendix A.

Based on the 'Final' analysis, 1 (<1%) placebo patients, 3 (1%) SC-58635 100 mg BID patients, 2 (<1%) SC-58635 200 mg BID patients, 1 (<1%) SC-58635 400 mg BID patients and 8 (4%) Naproxen 500 mg BID patients developed an ulcer. The incidence of ulceration was significantly greater in Naproxen 500 mg BID compared with all treatment groups including placebo ($p\leq0.039$) except for Naproxen compared to SC-58635 100 mg BID ($p=0.107$) and there were no statistically significant differences between placebo and any SC-58635 groups ($p\geq0.297$). Further, there was no statistically significant difference in the incidence of ulceration between any of the SC-58635 groups ($p\geq0.346$).

Based on the 'Week 12' analysis, ulcers developed in 1 (1%) placebo patients, 3 (2%) SC-58635 100 mg BID patients, 2 (1%) SC-58635 200 mg BID patients, 1 (1%) SC-

58635 400 mg BID patients, and 8 (6%) Naproxen 500 mg BID patients. The results of the pairwise comparisons were consistent with that of the 'Final' analysis.

Based on the Kaplan-Meier estimator, the rate of developing duodenal ulceration was greater for Naproxen than for placebo or any of the SC-58635 groups and this difference was statistically significant compared to the SC-58635 200 mg BID and 400 mg BID treatment groups ($p \leq 0.033$). There were no statistically significant differences between placebo and any of the SC-58635 groups ($p \geq 0.520$) and there were no statistically significant differences among any of the SC-58635 groups ($p \geq 0.383$).

2). Study 041

Gastroduodenal Endoscopy Results

The gastroduodenal endoscopy results described below are also presented in Table 18 of Appendix A.

Based on the 'Final' analysis, ulcers developed in 8 (4%) SC-58635 200 mg BID patients and 33 (15%) Diclofenac SR 75 mg BID patients. The comparison between the two treatments showed a statistically significant treatment difference ($p \leq 0.001$).

Based on the Kaplan-Meier estimator, the rate of developing gastroduodenal ulceration over 24 weeks was greater for Diclofenac SR 75 mg BID than for the SC-58635 200 mg BID group, and this difference was statistically significant ($p \leq 0.001$).

Gastric Endoscopy Results

The gastric endoscopy results described below are also presented in Table 19 of Appendix A.

Based on the 'Final' analysis, gastric ulcers developed in 5 (2%) SC-58635 200 mg BID patients and 24 (11%) Diclofenac 75 SR mg BID patients. The comparison between the two treatments showed a statistically significant treatment difference ($p=0.002$).

Based on the Kaplan-Meier curves, the rate of developing gastric ulceration over 24 weeks was greater for Diclofenac SR 75 mg BID-treated patients than for SC-58635 200 mg BID patients and this difference was statistically significant ($p \leq 0.001$).

Duodenal Endoscopy Results

The duodenal endoscopy results described below are also presented in Table 20 of Appendix A.

Based on the 'Final' analysis, ulcers developed in 4 (2%) SC-58635 200 mg BID patients and 15 (7%) Diclofenac SR 75 mg BID patients. The comparison between the two treatments showed a statistically significant treatment difference (p=0.003).

Based on the Kaplan-Meier estimator, the rate of developing duodenal ulceration over 24 weeks was greater for the Diclofenac SR group than for the SC-58635 group and this difference was statistically significant (p=0.007).

III. Reviewer's Comments

1. Improvement Rates for ACR Individual Components

Since the ACR Index is a composite measurement of the improvement of the ACR individual components, it is also of interest to know the improvement rate of each component. This reviewer classifies a patient 'Improved' in an ACR individual component if he/she has a 20% improvement from baseline in that component at Week 12. The results of improvement rate for each ACR component are presented in Tables 21-22 of Appendix A.

Recall that, in Study 022, the ACR improvement rates for placebo, SC-58635 100 mg BID, SC-58635 200 mg BID, SC-58635 400 mg BID and Naproxen 500 mg BID at Week 12 were 29%, 40%, 44%, 39% and 36%, respectively. Table 21 shows that the improvement rates for Patient's Global, Number of Tender/Painful Joints, Number of Swollen Joints, Physician's Global and Patient's Assessment of Pain are higher than and are with similar trend to ACR responder rate in all treatment arms. The improvement rates for HAQ Score are similar to the ACR improvement rates in all treatment arms. The improvement rates for CRP are lower than the ACR improvement rates in all treatment arms, and they are close to each other with a numerically higher improvement rate in the placebo group.

Recall that, in Study 023, the ACR improvement rates for placebo, SC-58635 100 mg BID, SC-58635 200 mg BID, SC-58635 400 mg BID and Naproxen 500 mg BID at Week 12 were 23%, 30%, 39%, 36% and 42%, respectively. Table 22 shows that the improvement rates for Patient's Global, Number of Tender/Painful Joints, Number of Swollen Joints, Physician's Global, Patient's Assessment of Pain and HAQ Score are higher than and are with similar trend to the ACR improvement rates in all treatment arms. The improvement rates for CRP are lower than the ACR improvement rates in all treatment arms, and are close to each other with a numerically higher improvement rate in the Naproxen group.

The fact that, in both Studies 022 and 023, the improvement rates of CRP are lower than the ACR Response Index, and are close to each other in all treatment arms shows that the CRP level was not responding to the treatments.

2. 'Week 12' Analysis vs. 'Final' Analysis for UGI Event Rates

As described in the **'GI Endpoints and Analyses Plan'** on page 8, both 'Week 12' analysis and 'Final' analysis were done for the crude rates of gastroduodenal ulcers in Study 022. The 'Week 12' analysis only included patients who either finished the 12 weeks treatment or developed ulcer before 12 weeks. Since there were less patients in the placebo group finished the 12 weeks study than in other treatment groups, the ulcer rate in the placebo arm was 'inflated' compared to that in other treatments. So the 'Week 12' analysis is biased against placebo. The 'Final' analysis is a last-observation-carried-forward analysis for all patients who underwent a endoscopy evaluation, so it is statistically and clinically more valid than the 'Week 12' analysis.

3. Patient Over-Enrollment in Study 041

In Study 041, the 49% over enrollment of patients (430 vs. 288) caused the Agency's concern. Per medical reviewer (GI part) Dr. Larry Goldkind's request, the Sponsor redid the GI analysis based on the first 288 patients recruited in the GI study, and the results were similar in terms of statistical significance to the original results based on the 430 patients. Please refer to Dr. Larry Goldkind's review for detailed results.

4. Ulcer Incidence along Time

In Study 022, the SC-58635 groups and Naproxen group showed a trend that gastroduodenal ulcer incidences were higher in the later stage that that in the beginning of the trial (Table 15 of Appendix A, Part 3), but there was no such a trend in the placebo group. This is also reflected by that the estimated ulcer incidences at Week 12 for the SC-58635 groups and Naproxen group (11.5% for SC-58635 100 mg BID, 7.5% for SC-58635 200 mg BID, 9.9% for SC-58635 400 mg BID, and 37.4% for Naproxen 500 mg BID (Figure 1)) were higher than the overall ulcer incidence (4% for SC-58635 100 mg BID, 3% for SC-58635 200 mg BID, 4% for SC-58635 400 mg BID and 18% for Naproxen 500 mg BID (Table 15 of Appendix A)). This would suggest that SC-58635 associated ulcers are less symptomatic than ulcers in patients not on any therapy, and a longer duration might be necessary to detect these ulcers.

IV. Final Conclusion

1. Efficacy in Treatment of RA

a. SC-58635 100 mg BID, SC-58635 200 mg BID and SC-58635 400 mg BID are efficacious in treating RA signs and symptoms. The ACR improvement rates in the three SC-58635 groups are statistically significantly higher than that in the placebo group in both Study 022 and Study 023.
b. Naproxen 500 mg BID is efficacious in treating RA signs and symptoms. The ACR improvement rate of Naproxen 500 mg BID is statistically higher than that in placebo

and not statistically different from SC-58635 200 mg BID and SC-58635 400 mg BID in both Study 022 and Study 023.

c. Although, in general, there were no statistically significant differences between SC-58635 100 mg BID, SC-58635 200 mg BID and SC-58635 400 mg BID, SC-58635 200 mg BID was numerically superior than SC-58635 100 mg BID in ACR improvement rate and all ACR individual components in both Study 022 and Study 023.

2. UGI Ulcer Rates

Study 022

a. The incidence of **gastroduodenal** ulceration were statistically significantly higher in the Naproxen 500 mg BID group than that in the placebo, 58635 100 mg BID, SC-58635 200 mg BID and SC-58635 400 mg BID groups. The incidences of **gastroduodenal** ulcer for the three SC-58635 groups were numerically higher than that of the placebo group, although the differences were not statistically significant. There was no statistically significant difference between any of the SC-58635 groups in the incidence of **gastroduodenal** ulceration. There was a trend that the incidences of **gastroduodenal** ulcers in the SC-58635 groups and Naproxen group were higher at the later stage than that in the beginning of the trial.

b. The incidences of **gastric** ulceration were statistically significantly higher in the Naproxen 500 mg BID group than that in the placebo, 58635 100 mg BID, SC-58635 200 mg BID and SC-58635 400 mg BID groups. There were no statistically significant differences in the incidence of **gastric** ulceration between placebo and the three SC-58635 groups. There was no statistically significant difference between any of the SC-58635 groups in the incidences of **gastric** ulceration.

c. The incidences of **duodenal** ulceration was statistically significantly greater in the Naproxen 500 mg BID group than the placebo, SC-58635 200 mg BID and SC-58635 400 mg BID groups, but no statistically significant difference was found between Naproxen 500 mg BID and SC-58635 100 mg BID. There were no statistically significant differences in the incidence of duodenal ulceration between placebo and the three SC-58635 groups. Also, there was no statistically significant difference between any of the SC-58635 groups.

Study 041

The incidences of gastroduodenal, gastric and duodenal ulceration of Diclofenac 75 mg BID group were statistically significantly higher than that in the SC-58635 200 mg BID group.

Laura Lu, Ph.D.
Mathematical Statistician

Concur:

Stan Lin, Ph.D.
Team Leader

APPEARS THIS WAY
ON ORIGINAL

CC:

HFD-550/MO/Witter
HFD-550/PM/Lutwak
HFD-550/MO/Hyde
HFD-550/Div. File
HFD-725/Lu
HFD-725/Lin ST.
HFD-725/Huque
HFD-725/Div. File

Appendix A. Tables

Table 1. Reasons for Study Termination (All Randomized Patients: 12-Week Pivotal Studies 022 and 023 and 12-Week Pooled Pivotal Studies)

	Number of Rheumatoid Arthritis Patients by Treatment Group				
		SC-58635			Naproxen
Study	Placebo	100 mg BID	200 mg BID	400 mg BID	500 mg BID
Study 022	**(n=231)**	**(n=240)**	**(n=235)**	**(n=218)**	**(n=225)**
Total Completed	**101 (44%)**	**154 (64%)**	**158 (67%)**	**137 (63%)**	**138 (61%)**
Total Withdrawn	**130 (56%)**	**86 (36%)**	**77 (33%)**	**81 (37%)**	**87 (39%)**
Lost to Follow-up	3 (1%)	1 (<1%)	3 (1%)	1(<1%)	1 (<1%)
Pre-Existing Violation	2 (<1%)	1 (<1%)	3 (1%)	2 (<1%)	0 (0%)
Protocol Non-Compliance	10 (4%)	4 (2%)	4 (2%)	7 (3%)	9 (4%)
Treatment Failure	104 (45%)	67 (28%)	50 (21%)	59 (27%)	65 (29%)
Adverse Event	11 (5%)	13 (5%)	17 (7%)	12 (6%)	12 (5%)
Study 023	**(n=221)**	**(n=228)**	**(n=219)**	**(n=217)**	**(n=218)**
Total Completed	**78(35%)**	**117 (51%)**	**124 (57%)**	**126 (58%)**	**133(61%)**
Total Withdrawn	**143 (65%)**	**111 (49%)**	**95 (43%)**	**91 (42%)**	**85(39%)**
Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)	2 (<1%)	0 (0%)
Pre-Existing Violation	2(<1%)	2 (<1%)	3 (1%)	2 (<1%)	0 (0%)
Protocol Non-Compliance	4 (2%)	5 (2%)	2 (<1%)	2 (<1%)	0 (0%)
Treatment Failure	125 (57%)	92 (40%)	74 (34%)	69 (32%)	69(32%)
Adverse Event	12 (5%)	12 (5%)	16 (7%)	16 (7%)	16 (7%)
Pooled [a]	**(n=452)**	**(n=468)**	**(n=454)**	**(n=435)**	**(n=443)**
Total Completed	**179 (40%)**	**271 (58%)**	**282 (62%)**	**263 (60%)**	**271 (61%)**
Total Withdrawn	**273 (60%)**	**197 (42%)**	**172 (38%)**	**172 (40%)**	**172 (39%)**
Lost to Follow-up	3 (<1%)	1 (<1%)	3 (<1%)	3 (<1%)	1 (<1%)
Pre-Existing Violation	4 (<1%)	3 (<1%)	6 (1%)	4 (<1%)	0 (0%)
Protocol Non-Compliance	14 (3%)	9 (2%)	6 (1%)	9 (2%)	9 (2%)
Treatment Failure	229 (51%)	159(34%)	124 (27%)	128 (29%)	134 (30%)
Adverse Event	23 (5%)	25 (5%)	33 (7%)	28 (6%)	28 (6%)

a) Pooled represents data from combined pivotal Studies 022 and 023.

APPEARS THIS WAY
ON ORIGINAL

Table 2. ACR-20 Responders Index: Categorical Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022, 023, and Pooled Pivotal Studies)

		Percent of Patients Who Improved or Did Not Improve		
Treatment Group	**Variable**	**Study 022**	**Study 023**	**Pooled(a)**
Baseline to Week 2				
Placebo	%Improved	22	25	23
	%Not Improved	78	75	77
SC-58635 100 mg BID	%Improved	40*	42*	41*
	%Not Improved	60	58	59
SC-58635 200 mg BID	%Improved	49* **	46*	48*
	%Not Improved	51	54	52
SC-58635 400 mg BID	%Improved	41*	43*	42*
	%Not Improved	59	57	58
Naproxen 500 mg BID	%Improved	40	44*	42*
	%Not Improved	60*	56	58
Baseline to Week 6				
Placebo	%Improved	28	27	27
	%Not Improved	72	73	73
SC-58635 100 mg BID	%Improved	39*	38*	38*
	%Not Improved	61	62	62
SC-58635 200 mg BID	%Improved	49* **	41*	45*
	%Not Improved	51	59	55
SC-58635 400 mg BID	%Improved	40*	43*	42*
	%Not Improved	60	57	58
Naproxen 500 mg BID	%Improved	37*	46*	42*
	%Not Improved	63	54	58
Baseline to Week 12				
Placebo	%Improved	29	23	26
	%Not Improved	71	77	74
SC-58635 100 mg BID	%Improved	40*	30 **	35*
	%Not Improved	60	70	65
SC-58635 200 mg BID	%Improved	44*	39*	42*
	%Not Improved	56	61	58
SC-58635 400 mg BID	%Improved	39*	36*	38*
	%Not Improved	61	64	62
Naproxen 500 mg BID	%Improved	36*	42*	39*
	%Not Improved	64	58	61

a) Pooled represents data combined from pivotal Studies 022 and 023.
* Indicates a statistically significant difference ($p<0.05$) from placebo.
** Indicates a statistically significant difference ($p<0.05$) from active comparator.

Table 3. Patient's Global Assessment of Arthritic Condition: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	3.8	3.7	3.7
SC-58635 100 mg BID	3.8	3.7	3.7
SC-58635 200 mg BID	3.8	3.7	3.7
SC-58635 400 mg BID	3.8	3.7	3.7
Naproxen 500 mg BID	3.7	3.7	3.7
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	3.3(-0.4)	3.4(-0.3)	3.3(-0.4)
SC-58635 100 mg BID	2.8(-0.9)*	2.9(-0.8)* **	2.9(-0.8)*
SC-58635 200 mg BID	2.7(-1.1)* **	2.8(-1.0)*	2.7(-1.0)*
SC-58635 400 mg BID	2.8(-1.0)*	2.8(-1.0)*	2.8(-1.0)*
Naproxen 500 mg BID	2.9(-0.9)*	2.7(-1.0)*	2.8(-0.9)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	3.3(-0.5)	3.4(-0.3)	3.3(-0.4)
SC-58635 100 mg BID	2.9(-0.8)*	3.0(-0.7)* **	3.0(-0.7)*
SC-58635 200 mg BID	2.8(-1.0)*	2.9(-0.8)*	2.8(-0.9)*
SC-58635 400 mg BID	2.8(-0.9)*	2.9(-0.8)*	2.9(-0.9)*
Naproxen 500 mg BID	2.9(-0.8)*	2.8(-0.9)*	2.9(-0.9)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	3.2(-0.5)	3.4(-0.3)	3.3(-0.4)
SC-58635 100 mg BID	2.9(-0.8)*	3.2(-0.6)* **	3.1(-0.7)* **
SC-58635 200 mg BID	2.8(-0.9)*	3.0(-0.8)*	2.9(-0.8)*
SC-58635 400 mg BID	2.9(-0.8)*	3.0(-0.7)*	3.0(-0.8)*
Naproxen 500 mg BID	3.0(-0.8)*	2.9(-0.9)*	2.9(-0.8)*

a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p<0.05$) from placebo.
** Indicates a statistically significant difference ($p<0.05$) from active comparator.

Text Table 4. Number of Tender/Painful Joints: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	29.2	30.1	28.7
SC-58635 100 mg BID	30.0	28.5	28.2
SC-58635 200 mg BID	31.4	29.7	29.6
SC-58635 400 mg BID	28.4	31.3	28.8
Naproxen 500 mg BID	28.9	29.8	28.2
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	21.7(-7.5)	23.2(-5.0)	22.5(-6.3)
SC-58635 100 mg BID	17.9(-11.3)*	17.7(-10.5)*	17.9(-10.9)*
SC-58635 200 mg BID	17.2(-12.0)*	16.2(-12.0)*	16.8(-12.0)*
SC-58635 400 mg BID	17.2(-12.0)*	16.5(-11.7)*	16.9(-11.8)*
Naproxen 500 mg BID	18.4(-10.8)*	16.5(-11.7)*	17.4(-11.3)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	21.0(-8.2)	23.0(-5.2)	21.8(-7.0)
SC-58635 100 mg BID	17.9(-11.3)*	17.7(-10.5)*	17.8(-10.9)*
SC-58635 200 mg BID	17.3(-11.9)*	17.6(-10.6)*	17.3(-11.4)*
SC-58635 400 mg BID	17.0(-12.2)*	16.9(-11.3)*	16.7(-12.0)*
Naproxen 500 mg BID	18.7(-10.5)*	16.7(-11.6)*	17.4(-11.3)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	21.0(-8.2)	22.7(-5.5)	21.9(-6.8)
SC-58635 100 mg BID	17.2(-12.0)*	18.2(-10.0)*	17.8(-10.9)*
SC-58635 200 mg BID	16.9(-12.3)*	18.0(-10.2)*	17.6(-11.2)*
SC-58635 400 mg BID	16.8(-12.4)*	17.1(-11.1)*	16.9(-11.8)*
Naproxen 500 mg BID	19.1(-10.1)	17.1(-11.2)*	18.1(-10.7)*

a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p<0.05$) from placebo.
** Indicates a statistically significant difference ($p<0.05$) from active comparator.

Table 5. Number of Swollen Joints: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	22.2	21.3	20.8
SC-58635 100 mg BID	21.0	21.4	20.5
SC-58635 200 mg BID	22.1	22.6	21.7
SC-58635 400 mg BID	20.8	22.3	20.7
Naproxen 500 mg BID	20.8	22.1	20.6
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	16.7(-4.6)	16.5(-3.9)	16.6(-4.2)
SC-58635 100 mg BID	14.3(-7.0)*	14.1(-6.3)*	14.2(-6.7)*
SC-58635 200 mg BID	13.3(-8.0)*	13.3(-7.1)*	13.2(-7.7)*
SC-58635 400 mg BID	14.4(-6.9)*	13.8(-6.6)*	14.2(-6.7)*
Naproxen 500 mg BID	14.5(-6.8)*	13.5(-6.8)*	14.0(-6.9)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	16.0(-5.4)	16.6(-3.8)	16.1(-4.8)
SC-58635 100 mg BID	13.7(-7.6)*	14.4(-5.9)*	14.0(-6.8)*
SC-58635 200 mg BID	12.4(-9.0)*	14.2(-6.2)*	13.1(-7.8)*
SC-58635 400 mg BID	13.3(-8.0)*	14.0(-6.4)*	13.5(-7.3)*
Naproxen 500 mg BID	13.4(-7.9)*	14.0(-6.4)*	13.5(-7.3)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	15.9(-5.5)	16.7(-3.7)	16.2(-4.6)
SC-58635 100 mg BID	13.3(-8.0)*	14.5(-5.9)*	14.0(-6.9)*
SC-58635 200 mg BID	12.2(-9.2)*	14.3(-6.0)*	13.2(-7.7)*
SC-58635 400 mg BID	13.7(-7.6)*	14.0(-6.4)*	13.9(-7.0)*
Naproxen 500 mg BID	13.8(-7.6)*	14.3(-6.1)*	14.0(-6.9)*

a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p<0.05$) from placebo.
** Indicates a statistically significant difference ($p<0.05$) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 6. Physician's Global Assessment of Arthritic Condition: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	3.7	3.6	3.6
SC-58635 100 mg BID	3.6	3.6	3.6
SC-58635 200 mg BID	3.8	3.6	3.7
SC-58635 400 mg BID	3.7	3.6	3.7
Naproxen 500 mg BID	3.6	3.7	3.6
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	3.2(-0.4)	3.3(-0.3)	3.2(-0.4)
SC-58635 100 mg BID	2.8(-0.8)*	2.9(-0.8)* **	2.8(-0.8)*
SC-58635 200 mg BID	2.6(-1.0)* **	2.7(-1.0)*	2.6(-1.0)*
SC-58635 400 mg BID	2.7(-0.9)*	2.8(-0.9)*	2.7(-0.9)*
Naproxen 500 mg BID	2.8(-0.8)*	2.7(-1.0)*	2.7(-0.9)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	3.1(-0.5)	3.3(-0.4)	3.2(-0.5)
SC-58635 100 mg BID	2.9(-0.8)*	3.0(-0.7)* **	2.9(-0.7)* **
SC-58635 200 mg BID	2.7(-1.0)* **	2.8(-0.8)*	2.7(-0.9)*
SC-58635 400 mg BID	2.7(-0.9)*	2.8(-0.8)*	2.8(-0.9)*
Naproxen 500 mg BID	2.9(-0.8)*	2.7(-0.9)*	2.8(-0.9)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	3.1(-0.5)	3.3(-0.3)	3.2(-0.4)
SC-58635 100 mg BID	2.9(-0.8)*	3.0(-0.6)* **	3.0(-0.7)*
SC-58635 200 mg BID	2.7(-0.9)* **	2.9(-0.8)*	2.8(-0.8)*
SC-58635 400 mg BID	2.8(-0.9)*	2.9(-0.8)*	2.8(-0.8)*
Naproxen 500 mg BID	2.9(-0.7)*	2.8(-0.9)*	2.9(-0.8)*

a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p<0.05$) from placebo.
** Indicates a statistically significant difference ($p<0.05$) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 7. Patient's Assessment of Pain-Visual Analog Scale (VAS): LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	70.2	68.5	68.5
SC-58635 100 mg BID	68.1	66.6	66.4
SC-58635 200 mg BID	69.8	68.3	68.1
SC-58635 400 mg BID	67.3	68.3	66.8
Naproxen 500 mg BID	68.1	67.2	66.6
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	59.8(-7.5)	58.5(-8.8)	59.3(-8.0)
SC-58635 100 mg BID	44.5(-22.7)*	46.6(-20.7)* **	45.9(-21.4)*
SC-58635 200 mg BID	40.1(-27.2)* **	41.3(-26.0)*	40.8(-26.5)*
SC-58635 400 mg BID	43.3(-24.0)*	42.3(-25.1)*	42.9(-24.4)*
Naproxen 500 mg BID	44.6(-22.7)*	41.2(-26.1)*	43.1(-24.2)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	58.4(-8.9)	61.2(-6.1)	59.4(-7.9)
SC-58635 100 mg BID	49.4(-17.9)*	49.0(-18.3)*	49.1(-18.2)*
SC-58635 200 mg BID	43.3(-24.0)* **	47.0(-20.4)*	44.8(-22.5)*
SC-58635 400 mg BID	47.2(-20.1)*	46.2(-21.1)*	46.5(-20.8)*
Naproxen 500 mg BID	48.2(-19.1)*	44.8(-22.5)*	46.2(-21.1)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	58.0(-9.3)	61.8(-5.5)	60.1(-7.2)
SC-58635 100 mg BID	49.0(-18.2)*	51.8(-15.5)* **	50.9(-16.4)*
SC-58635 200 mg BID	46.2(-21.1)*	46.9(-20.4)*	46.9(-20.4)*
SC-58635 400 mg BID	47.6(-19.7)*	48.9(-18.5)*	48.5(-18.8)*
Naproxen 500 mg BID	49.1(-18.2)*	45.3(-22.0)*	47.5(-19.8)*

a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p<0.05$) from placebo.
** Indicates a statistically significant difference ($p<0.05$) from active comparator.

Table 8. Health Assessment Questionnaire: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	1.45	1.42	1.39
SC-58635 100 mg BID	1.43	1.44	1.38
SC-58635 200 mg BID	1.52	1.38	1.40
SC-58635 400 mg BID	1.44	1.35	1.35
Naproxen 500 mg BID	1.51	1.43	1.43
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	1.38(-0.04)	1.29(-0.07)	1.34(-0.04)
SC-58635 100 mg BID	1.19(-0.23)*	1.12(-0.24)*	1.17(-0.22)*
SC-58635 200 mg BID	1.14(-0.28)* **	1.05(-0.31)*	1.11(-0.28)*
SC-58635 400 mg BID	1.11(-0.30)* **	1.06(-0.30)*	1.10(-0.29)* **
Naproxen 500 mg BID	1.22(-0.20)*	1.08(-0.28)*	1.16(-0.23)*
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	1.31(-0.11)	1.30(-0.06)	1.31(-0.08)
SC-58635 100 mg BID	1.22(-0.20)*	1.18(-0.18)*	1.21(-0.18)* **
SC-58635 200 mg BID	1.12(-0.30)*	1.08(-0.28)*	1.11(-0.28)*
SC-58635 400 mg BID	1.13(-0.29)*	1.10(-0.26)*	1.12(-0.26)*
Naproxen 500 mg BID	1.17(-0.25)*	1.10(-0.26)*	1.14(-0.25)*
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	1.32(-0.10)	1.29(-0.07)	1.32(-0.07)
SC-58635 100 mg BID	1.24(-0.17)	1.22(-0.14) **	1.25(-0.14)* **
SC-58635 200 mg BID	1.12(-0.30)*	1.12(-0.24)*	1.14(-0.25)*
SC-58635 400 mg BID	1.13(-0.29)*	1.11(-0.25)*	1.14(-0.25)*
Naproxen 500 mg BID	1.20(-0.22)*	1.11(-0.25)*	1.17(-0.22)*

a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p<0.05$) from placebo.
** Indicates a statistically significant difference ($p<0.05$) from active comparator.

Table 9. C-Reactive Protein: LS Mean Score and LS Mean Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022 and 023 and Pooled 12-Week Pivotal Studies)

Treatment Group	Study 022	Study 023	Pooled(a)
Baseline LS Mean Score			
Placebo	16901	15894	15986
SC-58635 100 mg BID	15532	16922	15857
SC-58635 200 mg BID	17214	18470	17310
SC-58635 400 mg BID	16705	16011	15792
Naproxen 500 mg BID	15248	16090	15051
Week 2 LS Mean Score (Change from Baseline to Week 2)(b)			
Placebo	16240(433.3)	15905(-300.7)	15965(-38.6)
SC-58635 100 mg BID	15642(-165.2)	16909(703.6)	16206(202.3)
SC-58635 200 mg BID	15516(-290.6)	16580(374.8)	15879(-124.3)
SC-58635 400 mg BID	18027(2220.3) **	17741(1535.4) **	17824(1820.0)* **
Naproxen 500 mg BID	14526(-1281)	14958(-1247)	14676(-1328)
Week 6 LS Mean Score (Change from Baseline to Week 6)(b)			
Placebo	16304(497.3)	17625(1420.0)	16814(810.1)
SC-58635 100 mg BID	17356(1548.8)	18312(2106.5)	17784(1780.7) **
SC-58635 200 mg BID	16039(232.1)	16601(395.5)	16211(206.9)
SC-58635 400 mg BID	19073(3266.2) **	20077(3871.3) **	19386(3382.8)* **
Naproxen 500 mg BID	15545(-261.7)	15865(-340.8)	15623(-380.7)
Week 12 LS Mean Score (Change from Baseline to Week 12)(b)			
Placebo	16788(981.3)	18984(2778.4)	17863(1858.9)
SC-58635 100 mg BID	17102(1294.9)	17442(1236.1)	17123(1119.7)
SC-58635 200 mg BID	16943(1135.6)	16243(37.6)	16454(450.2)
SC-58635 400 mg BID	19382(3574.8)	19195(2990.0) **	19165(3161.7) **
Naproxen 500 mg BID	16691(884.3)	14936(-1270)*	15761(-243.1)

a) Pooled represents data combined from pivotal Studies 022 and 023.
b) Values are least square mean change. Negative values signify improvement.
* Indicates a statistically significant difference ($p<0.05$) from placebo.
** Indicates a statistically significant difference ($p<0.05$) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 10. ACR-50 Responders Index: Categorical Change from Baseline (ITT Cohort: 12-Week Pivotal Studies 022, and 023)

		Percent of Patients Who Improved or Did Not Improve	
Treatment Group	**Variable**	**Study 022**	**Study 023**
Baseline to Week 2			
Placebo	%Improved	6	5
	%Not Improved	94	95
SC-58635 100 mg BID	%Improved	9	11*
	%Not Improved	91	89
SC-58635 200 mg BID	%Improved	15*	17*
	%Not Improved	85	83
SC-58635 400 mg BID	%Improved	16*	12*
	%Not Improved	84	88
Naproxen 500 mg BID	%Improved	12*	15*
	%Not Improved	88	85
Baseline to Week 6			
Placebo	%Improved	8	7
	%Not Improved	92	93
SC-58635 100 mg BID	%Improved	12	10
	%Not Improved	88	90
SC-58635 200 mg BID	%Improved	17*	16*
	%Not Improved	83	84
SC-58635 400 mg BID	%Improved	17*	12
	%Not Improved	83	88
Naproxen 500 mg BID	%Improved	13*	15*
	%Not Improved	87	85
Baseline to Week 12			
Placebo	%Improved	7	6
	%Not Improved	93	94
SC-58635 100 mg BID	%Improved	11	10**
	%Not Improved	89	90
SC-58635 200 mg BID	%Improved	17*	17*
	%Not Improved	83	83
SC-58635 400 mg BID	%Improved	17*	12*
	%Not Improved	83	88
Naproxen 500 mg BID	%Improved	13	18*
	%Not Improved	87	82

* Indicates a statistically significant difference ($p<0.05$) from placebo.

** Indicates a statistically significant difference ($p<0.05$) from active comparator.

APPEARS THIS WAY
ON ORIGINAL

Table 11. Number of Subjects in Pivotal Studies Reporting All-Causalities Adverse Events for Only Adverse Events Not Associated With Medical History Events --RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452 N	(%)	100mg BID N = 468 N	(%)	200mg BID N = 454 N	(%)	400mg BID N = 435 N	(%)	Naproxan N = 443 N	(%)	P-Value
APPLICATION SITE DISORDERS											
CELLULITIS	0	(0.0)	0	(0.0)	1	(0.2)	4	(0.9)	2	(0.5)	0.029
BODY AS A WHOLE - GENERAL DISORDERS											
BACK PAIN	17	(3.8)	12	(2.6)	11	(2.4)	4	(0.9)	4	(0.9)	0.001
EDEMA GENERALIZED	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.2)	5	(1.1)	0.006
PAIN	6	(1.3)	4	(0.9)	4	(0.9)	2	(0.5)	1	(0.2)	0.045
PERIPHERAL PAIN	6	(1.3)	7	(1.5)	4	(0.9)	2	(0.5)	2	(0.5)	0.052
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM	118	(26.1)	102	(21.8)	95	(20.9)	84	(19.3)	85	(19.2)	0.008
APHASIA	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
ATAXIA	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
CONVULSIONS	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
CRAMPS LEGS	1	(0.2)	2	(0.4)	4	(0.9)	3	(0.7)	5	(1.1)	0.086
DIZZINESS	10	(2.2)	6	(1.3)	9	(2.0)	9	(2.1)	15	(3.4)	0.149
DYSKINESIA	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
DYSPHONIA	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
HEADACHE	100	(22.1)	78	(16.7)	77	(17.0)	66	(15.2)	62	(14.0)	0.002
HYPERKINESIA	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0.467
HYPERTONIA	4	(0.9)	5	(1.1)	3	(0.7)	2	(0.5)	0	(0.0)	0.042
HYPOESTHESIA	1	(0.2)	3	(0.6)	2	(0.4)	1	(0.2)	0	(0.0)	0.303
MIGRAINE	6	(1.3)	8	(1.7)	0	(0.0)	2	(0.5)	2	(0.5)	0.022
NEURALGIA	2	(0.4)	3	(0.6)	4	(0.9)	4	(0.9)	4	(0.9)	0.353
NEURITIS	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0.467
NEUROPATHY	0	(0.0)	0	(0.0)	2	(0.4)	1	(0.2)	0	(0.0)	0.662
PARESTHESIA	5	(1.1)	5	(1.1)	1	(0.2)	3	(0.7)	2	(0.5)	0.174
VERTIGO	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0	(0.0)	0.498
VISUAL FIELD DEFECT	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0.487
GASTRO-INTESTINAL SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM	84	(18.6)	118	(25.2)	110	(24.2)	109	(25.1)	130	(29.3)	0.001
ABDOMINAL PAIN	12	(2.7)	19	(4.1)	13	(2.9)	15	(3.4)	26	(5.9)	0.042
BOWEL DISEASE	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
CHEILITIS	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
COLITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
CONSTIPATION	13	(2.9)	7	(1.5)	8	(1.8)	3	(0.7)	13	(2.9)	0.746
DIARRHEA	18	(4.0)	26	(5.6)	24	(5.3)	28	(6.4)	18	(4.1)	0.755
DIVERTICULITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
DYSPEPSIA	29	(6.4)	47	(10.0)	40	(8.8)	38	(8.7)	55	(12.4)	0.014
DYSPHAGIA	2	(0.4)	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0.589
ERUCTATION	1	(0.2)	0	(0.0)	1	(0.2)	2	(0.5)	0	(0.0)	0.974
ESOPHAGITIS	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0	(0.0)	0.498
FLATULENCE	3	(0.7)	13	(2.8)	10	(2.2)	8	(1.8)	8	(1.8)	0.511

Table 11. (Continue) Number of Subjects in Pivotal Studies Reporting All-Causalities Adverse Events for Only Adverse Events Not Associated With Medical History Events --RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452 N	(%)	100mg BID N = 468 N	(%)	200mg BID N = 454 N	(%)	400mg BID N = 435 N	(%)	Naproxan N = 443 N	(%)	P-Value
GASTRO-INTESTINAL SYSTEM DISORDERS											
GASTRIC ULCER	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.2)	0.305
GASTRITIS	0	(0.0)	1	(0.2)	2	(0.4)	4	(0.9)	0	(0.0)	0.397
GASTROENTERITIS	4	(0.9)	5	(1.1)	2	(0.4)	4	(0.9)	2	(0.5)	0.426
GASTROESOPHAGEAL REFLUX	0	(0.0)	3	(0.6)	4	(0.9)	3	(0.7)	4	(0.9)	0.114
GI NEOPLASM BENIGN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
GINGIVITIS	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.2)	0.305
H PYLORI	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0.631
HEMORRHAGE RECTUM	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
HEMORRHOIDS	1	(0.2)	2	(0.4)	0	(0.0)	0	(0.0)	1	(0.2)	0.497
HEMORRHOIDS BLEEDING	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
HERNIA	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.047
HIATAL HERNIA	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	0.599
HICCUP	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.5)	0	(0.0)	0.304
MELENA	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0.632
NAUSEA	23	(5.1)	18	(3.8)	15	(3.3)	18	(4.1)	18	(4.1)	0.550
SALIVARY GLAND ENLARGEMENT	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0.467
STOMATITIS	4	(0.9)	7	(1.5)	4	(0.9)	1	(0.2)	11	(2.5)	0.237
STOOLS ABNORMAL	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.5)	0	(0.0)	0.304
TONGUE DISORDER	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0.487
TOOTH CARIES	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0.600
TOOTH DISORDER	6	(1.3)	9	(1.9)	9	(2.0)	8	(1.8)	5	(1.1)	0.799
VOMITING	5	(1.1)	4	(0.9)	4	(0.9)	11	(2.5)	6	(1.4)	0.207
LIVER AND BILIARY SYSTEM DISORDERS											
HEPATIC FUNCTION ABNORMAL	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.047
REPRODUCTIVE DISORDERS, FEMALE											
DYSMENORRHEA	5	(1.1)	4	(0.9)	2	(0.4)	3	(0.7)	0	(0.0)	0.042
REPRODUCTIVE DISORDERS, MALE											
INFECTION SOFT TISSUE	1	(0.2)	1	(0.2)	4	(0.9)	2	(0.5)	6	(1.4)	0.032

Table 12. Number of Subjects in Pivotal Studies Reporting Treatment-Related Adverse Events
RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452 N	(%)	100mg BID N = 468 N	(%)	200mg BID N = 454 N	(%)	400mg BID N = 435 N	(%)	Naproxan N = 443 N	(%)	P-Value
BODY AS A WHOLE - GENERAL DISORDERS											
BACK PAIN	4	(0.9)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0.010
EDEMA GENERALIZED	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	5	(1.1)	0.001
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS											
HEADACHE	39	(8.6)	34	(7.3)	31	(6.8)	24	(5.5)	25	(5.6)	0.040
GASTRO-INTESTINAL SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM	60	(13.3)	81	(17.3)	79	(17.4)	70	(16.1)	97	(21.9)	0.004
ABDOMINAL PAIN	11	(2.4)	16	(3.4)	10	(2.2)	11	(2.5)	21	(4.7)	0.151
BOWEL DISEASE	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
COLITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
CONSTIPATION	6	(1.3)	3	(0.6)	5	(1.1)	2	(0.5)	11	(2.5)	0.187
DIARRHEA	12	(2.7)	21	(4.5)	17	(3.7)	17	(3.9)	12	(2.7)	0.858
DIVERTICULITIS	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
DYSPEPSIA	24	(5.3)	39	(8.3)	34	(7.5)	30	(6.9)	44	(9.9)	0.049
DYSPHAGIA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
ERUCTATION	1	(0.2)	0	(0.0)	1	(0.2)	2	(0.5)	0	(0.0)	0.974
ESOPHAGITIS	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0	(0.0)	0.498
FLATULENCE	3	(0.7)	8	(1.7)	7	(1.5)	6	(1.4)	8	(1.8)	0.271
GASTRIC ULCER	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	1	(0.2)	0.305
GASTRITIS	0	(0.0)	1	(0.2)	2	(0.4)	3	(0.7)	0	(0.0)	0.536
GASTROENTERITIS	1	(0.2)	1	(0.2)	2	(0.4)	0	(0.0)	0	(0.0)	0.302
GASTROESOPHAGEAL REFLUX	0	(0.0)	3	(0.6)	3	(0.7)	2	(0.5)	2	(0.5)	0.469
HEMORRHAGE RECTUM	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
HEMORRHOIDS	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.160
HEMORRHOIDS BLEEDING	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
HIATAL HERNIA	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	1	(0.2)	0.599
HICCUP	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.5)	0	(0.0)	0.304
MELENA	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
NAUSEA	16	(3.5)	13	(2.8)	11	(2.4)	14	(3.2)	12	(2.7)	0.626
STOMATITIS	3	(0.7)	3	(0.6)	3	(0.7)	0	(0.0)	9	(2.0)	0.115
STOOLS ABNORMAL	0	(0.0)	0	(0.0)	0	(0.0)	2	(0.5)	0	(0.0)	0.304
VOMITING	2	(0.4)	3	(0.6)	3	(0.7)	5	(1.1)	1	(0.2)	0.952
LIVER AND BILIARY SYSTEM DISORDERS											
HEPATIC FUNCTION ABNORMAL	2	(0.4)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0.047
SYCHIATRIC DISORDERS											
INSOMNIA	0	(0.0)	3	(0.6)	6	(1.3)	2	(0.5)	8	(1.8)	0.012
VISION DISORDERS											
BLURRED VISION	2	(0.4)	5	(1.1)	1	(0.2)	0	(0.0)	0	(0.0)	0.027

Table 13. Number of Subjects in Pivotal Studies Reporting All-Causalities Adverse Events for Only Severe Adverse Events
RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452 N	(%)	100mg BID N = 468 N	(%)	200mg BID N = 454 N	(%)	400mg BID N = 435 N	(%)	Naproxan N = 443 N	(%)	P-Value
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	13	(2.9)	5	(1.1)	5	(1.1)	4	(0.9)	5	(1.1)	0.040
ALL TERMS IN BODY SYSTEM	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
ATAXIA	0	(0.0)	0	(0.0)	2	(0.4)	0	(0.0)	2	(0.5)	0.147
DIZZINESS	12	(2.7)	4	(0.9)	2	(0.4)	3	(0.7)	2	(0.5)	0.002
HEADACHE	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0.487
MIGRAINE	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0.600
NEURALGIA	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.982
PARESTHESIA											
GASTRO-INTESTINAL SYSTEM DISORDERS	5	(1.1)	8	(1.7)	8	(1.8)	5	(1.1)	15	(3.4)	0.045
ALL TERMS IN BODY SYSTEM	1	(0.2)	3	(0.6)	1	(0.2)	1	(0.2)	6	(1.4)	0.090
ABDOMINAL PAIN	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	1	(0.2)	0.971
DIARRHEA	3	(0.7)	1	(0.2)	2	(0.4)	2	(0.5)	6	(1.4)	0.164
DYSPEPSIA	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
GASTRIC ULCER	1	(0.2)	2	(0.4)	0	(0.0)	0	(0.0)	1	(0.2)	0.497
GASTROENTERITIS	0	(0.0)	1	(0.2)	3	(0.7)	1	(0.2)	2	(0.5)	0.265
NAUSEA	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0.150
STOMATITIS	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
TOOTH CARIES	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0	(0.0)	0.632
TOOTH DISORDER	0	(0.0)	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	0.600
VOMITING											

Table 14. Number of Subjects in Pivotal Studies Reporting Treatment-Related Adverse Events for Only Severe Adverse Events
RA studies 22 and 23

Body System ICD-9 Term	Placebo N = 452		100mg BID N = 468		200mg BID N = 454		400mg BID N = 435		Naproxan N = 443		P-Value
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
GASTRO-INTESTINAL SYSTEM DISORDERS											
ALL TERMS IN BODY SYSTEM	3	(0.7)	4	(0.9)	7	(1.5)	4	(0.9)	11	(2.5)	0.027
ABDOMINAL PAIN	1	(0.2)	2	(0.4)	1	(0.2)	1	(0.2)	4	(0.9)	0.218
DIARRHEA	0	(0.0)	1	(0.2)	1	(0.2)	0	(0.0)	1	(0.2)	0.662
DYSPEPSIA	2	(0.4)	1	(0.2)	2	(0.4)	2	(0.5)	6	(1.4)	0.067
GASTRIC ULCER	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987
NAUSEA	0	(0.0)	1	(0.2)	3	(0.7)	1	(0.2)	2	(0.5)	0.265
VOMITING	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0.987

Table 15. ANALYSIS OF GASTRODUODENAL CRUDE ULCER RATE (Study 022)

Part 1: Ulcer Rate

	Placebo	SC-58635 100mg	SC-58635 200mg	SC-58635 400mg	Naproxan 500mg
	(N=231)	(N=240)	(N=235)	(N=217)	(N=225)
Week12 Analysis					
Known Results					
No ulcer	95(96%)	139(94%)	139(96%)	122(94%)	101(74%)
Ulcer	4(4%)	9(6%)	6(4%)	8(6%)	36(26%)
Unknown Results (Without Endo /With Endo)	132(36/96)	92(22/70)	90(28/62)	87(24/63)	88(22/66)
Final Analysis					
No Ulcer	196(98%)	214(96%)	213(97%)	189(96%)	173(82%)
Ulcer	4(2%)	9(4%)	6(3%)	8(4%)	37(18%)
Unknown	31(31/0)	17(17/0)	16(16/0)	20(20/0)	15(15/0)

Part 2: p- VALUES FOR TREATMENT COMPARISONS (a):

	200mg vs. Placebo	400mg vs. placebo	100mg vs. placebo	200mg vs. 100mg	400mg vs. 100gm	400mg vs. 200mg	Naproxen vs. placebo	Naproxen vs. 100mg	Naproxen vs. 200mg	Naproxen vs. 400mg
Week12	0.829	0.434	0.482	0.554	0.883	0.666	<0.001	<0.001	<0.001	<0.001
Final	0.539	0.230	0.200	0.526	0.966	0.582	<0.001	<0.001	<0.001	<0.001

(a) Cochran- Mantel- Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Part 3: NUMBER OF PATIENTS WITH ENDOSCOPY PERFORMED BY TIME INTERVAL

	Placebo		SC-58635 100mg		SC-58635 200mg		SC-58635 400mg		Naproxan 500mg	
	(N=231)		(N=240)		(N=235)		(N=217)		(N=225)	
Study Days	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer	No Ulcer	Ulcer
WK2 (2- 28)	64	1	31	1	28	1	28	0	27	8
WK6 (29- 76)	32	1	39	1	34	1	35	1	39	5
WK12 (77- 91)	95	2	139	7	139	4	122	7	101	23
>91	5	0	5	0	12	0	4	0	6	1
TOTAL	196	4	214	9	213	6	189	8	173	37

Table 16. ANALYSIS OF GASTRIC CRUDE ULCER RATE (Study 022)

Part 1: Ulcer Rate

	Placebo	SC-58635 100mg	SC-58635 200mg	SC-58635 400mg	Naproxan 500mg
	(N=231)	(N=240)	(N=235)	(N=217)	(N=225)
Week12 Analysis					
Known Results					
Noulcer	96(97%)	141(96%)	140(97%)	123(95%)	105(78%)
Ulcer	3(3%)	6(4%)	4(3%)	7(5%)	29(22%)
Unknown Results (Without Endo /With Endo)	132(36/96)	93(22/71)	91(28/63)	87(24/63)	91(22/69)
Final Analysis					
Noulcer	197(99%)	217(97%)	215(98%)	190(96%)	180(86%)
Ulcer	3(2%)	6(3%)	4(2%)	7(4%)	30(14%)
Unknown	31(31/0)	17(17/0)	16(16/0)	20(20/0)	15(15/0)

Part 2: p- VALUES FOR TREATMENT COMPARISONS (a):

	200mg vs. Placebo	400mg vs. placebo	100mg vs. placebo	200mg vs. 100mg	400mg vs. 100gm	400mg vs. 200mg	Naproxen vs. placebo	Naproxen vs. 100mg	Naproxen vs. 200mg	Naproxen vs. 400mg
WEEK12	0.828	0.409	0.717	0.550	0.607	0.477	<0.001	<0.001	<0.001	<0.001
FINAL	0.861	0.254	0.412	0.570	0.710	0.404	<0.001	<0.001	<0.001	<0.001

(a) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Table 17. ANALYSIS OF DUODENAL CRUDE ULCER RATE (Study 022)

Part 1: Ulcer Rate

	Placebo	SC-58635 100mg	SC-58635 200mg	SC-58635 400mg	Naproxan 500mg
	(N=231)	(N=240)	(N=235)	(N=217)	(N=225)
Week12 Analysis					
Known Results					
Noulcer	96(99%)	144(98%)	142(99%)	128(99%)	120(94%)
Ulcer	1(1%)	3(2%)	2(1%)	1(<1%)	8(6%)
Unknown Results (Without Endo /With Endo)	134(36/98)	93(22/71)	91(28/63)	88(24/64)	97(22/75)
Final Analysis					
Noulcer	199(>99%)	220(99%)	217(99%)	196(99%)	202(96%)
Ulcer	1(<1%)	3(1%)	2(<1%)	1(<1%)	8(4%)
Unknown	31(31/0)	17(17/0)	16(16/0)	20(20/0)	15(15/0)

Part 2: p- VALUES FOR TREATMENT COMPARISONS (a):

	200mg vs. Placebo	400mg vs. placebo	100mg vs. placebo	200mg vs. 100mg	400mg vs. 100gm	400mg vs. 200mg	Naproxen vs. placebo	Naproxen vs. 100mg	Naproxen vs. 200mg	Naproxen vs. 400mg
WEEK12	0.583	0.789	0.428	0.574	0.360	0.534	0.026	0.084	0.033	0.019
FINAL	0.510	0.784	0.297	0.598	0.346	0.537	0.011	0.107	0.039	0.019

(a) Cochran-Mantel-Haenszel test of treatment comparison stratified by baseline status (p-value from Row Mean Scores Differ), 'unknown' patients are excluded from the analysis

Table 18. GASTRODUODENAL ENDOSCOPY RESULTS by 'Final' Analysis (Study 041)

	SC-58635200mg	DICLOFENAC75MG	p-VALUE(a)
	(N=326)	(N=329)	
CRUDEULCERRATE:			<0.001
NOULCER	204(96%)	185(85%)	
ULCER	8(4%)	33(15%)	
TOTAL	212(100%)	218(100%)	

(a) Cochran-Mantel-Haenszel test stratified by center (p-value from Row Mean Scores Differ)

Table 19. GASTIC ENDOSCOPY RESULTS by 'Final' Analysis (Study 041)

	SC-58635200mg	DICLOFENAC75MG	p-VALUE(a)
	(N=326)	(N=329)	
CRUDEULCERRATE:			<0.002
NOULCER	207(98%)	194(89%)	
ULCER	5(2%)	24(11%)	
TOTAL	212(100%)	218(100%)	

(a) Cochran-Mantel-Haenszel test stratified by center (p-value from Row Mean Scores Differ)

Table 20. DUODENAL ENDOSCOPY RESULTS by 'Final' Analysis (Study 041)

	SC-58635200mg	DICLOFENAC75MG	p-VALUE(a)
	(N=326)	(N=329)	
CRUDEULCERRATE:			<0.003
NOULCER	208(98%)	202(93%)	
ULCER	4(2%)	15(7%)	
TOTAL	212(100%)	217(100%)	

(a) Cochran-Mantel-Haenszel test stratified by center (p-value from Row Mean Scores Differ)

Table 21. Study 022: Number and Percent of Patients Improved in ACR Individual Components (a)

	Placebo N(%)	SC-58635 100 N(%)	SC-58635 200 N(%)	SC-58635 400 N(%)	Naproxan 500 N(%)
Patient's Global	109 (47.19)	144(60.00)	148(62.98)	133(61.29)	130(57.78)
No. of Tender Joints	125(54.11)	170(70.83)	168(71.49)	153(70.51)	152(67.56)
No. of Swollen Joints	128(55.41)	160(66.67)	170(72.34)	139(64.06)	146(64.89)
Physician's Global	107(46.32)	137(57.08)	154(65.53)	135(62.21)	126(56.00)
Assessment of Pain	90(38.96)	129(53.75)	130(55.32)	121(55.76)	111(49.33)
HAQ Score	84(36.36)	95(39.58)	113(48.09)	97(44.70)	78(34.67)
CRP	55(23.81)	56(23.33)	47(20.00)	38(17.51)	36(16.00)

(a) A patient is classified as 'Improved' in a ACR individual component if the patient had at least 20% improvement from baseline in that component

Table 22. Study 023: Number and Percent of Patients Improved in ACR Individual Components (a)

	Placebo N(%)	SC-58635 100 N(%)	SC-58635 200 N(%)	SC-58635 400 N(%)	Naproxan 500 N(%)
Patient's Global	88(39.82)	116(50.88)	126(57.80)	126(58.06)	139(63.76)
No. of Tender Joints	108(48.87)	146(64.04)	143(65.60)	156(71.89)	153(70.18)
No. of Swollen Joints	120(54.30)	129(56.58)	146(66.97)	137(63.13)	137(62.84)
Physician's Global	80(36.20)	123(53.95)	126(57.80)	135(62.21)	148(67.89)
Assessment of Pain	78(35.29)	116(50.88)	118(54.13)	115(53.00)	132(60.55)
HAQ Score	69(31.22)	89(39.04)	98(44.95)	91(41.94)	98(44.95)
CRP	42(19.00)	52(22.81)	46(21.10)	45(20.74)	52(23.85)

(a) A patient is classified as 'Improved' in a ACR individual component if the patient had at least 20% improvement from baseline in that component

Appendix B. Figures

Figure 1. Kaplan-Meier Estimates of Gastroduodenal Ulcer Rate (Study 022)